ANTIOXIDANT VITAMINS C AND E IN MIGRAINE: A NARRATIVE REVIEW

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Abstract
Background: Although the pathophysiology of migraine is still unclear, oxidative stress is implicated as part of the mechanism, while several studies have reported a redox imbalance in migraine patients.
Objective: This narrative review examines the role of the antioxidant vitamins C and E in the treatment of migraine.
Results: Observational studies suggest that increased—but balanced—consumption of dietary antioxidants, including vitamins C and E, resulted in a lower risk of migraine and a lower frequency and severity of migraine attacks, especially in women of reproductive age. In addition, other observational studies and one randomised trial provide evidence that vitamin C supplementation (when taken alone or concomitantly with other antioxidants) may be beneficial for migraine outcomes in terms of frequency, duration, and intensity. However, a cross-sectional study from Taiwan reported an increase in migraine attacks in women taking vitamin C supplements. As for vitamin E, its antioxidant and anti-inflammatory properties may help control some migraine symptoms, particularly those associated with menstrual migraine.
Conclusions: Overall, the current evidence offers some hope for the use of vitamins C and E in the treatment of migraine. Future research and randomised controlled trials may help identifying dosing and specific patient groups who might benefit from vitamin C and E supplementation.

Keywords: migraine, antioxidants, supplements, vitamin C, vitamin E

ΑΝΤΙΟΞΕΙΔΩΤΙΚΕΣ ΒΙΤΑΜΙΝΕΣ C ΚΑΙ Ε ΣΤΗΝ ΗΜΙΚΡΑΝΙΑ: ΜΙΑ ΑΦΗΓΗΜΑΤΙΚΗ ΑΝΑΣΚΟΠΗΣΗ

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Περίληψη
Ιστορικό: Παρόλο που η παθοφυσιολογία της ημικρανίας είναι ακόμη ασαφής, το οξειδωτικό στρες εμπλέκεται ως μέρος του μηχανισμού, ενώ αρκετές μελέτες έχουν αναφέρει μια οξειδοαναγωγική ανισορροπία σε ασθενείς με ημικρανία.
Σκοπός: Αυτή η αφηγηματική ανασκόπηση εξετάζει τον ρόλο των αντιοξειδωτικών βιταμινών C και Ε στη θεραπεία της ημικρανίας.
Αποτελέσματα: Παρατηρητικές μελέτες υποδηλώνουν ότι η αυξημένη - αλλά ισορροπημένη - κατανάλωση διαιτητικών αντιοξειδωτικών, συμπεριλαμβανομένων των βιταμινών C και Ε, είχε ως αποτέλεσμα χαμηλότερο κίνδυνο ημικρανίας και χαμηλότερη συχνότητα και σοβαρότητα των κρίσεων ημικρανίας, ειδικά σε γυναίκες αναπαραγωγικής ηλικίας. Επιπλέον, άλλες παρατηρητικές μελέτες και μία τυχαιοποιημένη δοκιμή παρέχουν στοιχεία ότι η βιταμίνης C (όταν λαμβάνεται μόνη της ή ταυτόχρονα με άλλα αντιοξειδωτικά) μπορεί να είναι ευεργετική για τα αποτελέσματα της ημικρανίας όσον αφορά τη συχνότητα, τη διάρκεια και την ένταση. Ωστόσο, μια συγχρονική μελέτη από την Ταϊβάν ανέφερε αύξηση των κρίσεων ημικρανίας σε γυναίκες που λαμβάνουν συμπληρώματα βιταμίνης C. Όσον αφορά τη βιταμίνη Ε, οι αντιοξειδωτικές και αντιφλεγμονώδεις ιδιότητές της μπορεί να βοηθήσουν στον έλεγχο ορισμένων συμπτωμάτων ημικρανίας, ιδιαίτερα εκείνων που σχετίζονται με την ημικρανία της περιόδου.
Συμπεράσματα: Συνολικά, τα τρέχοντα στοιχεία προσφέρουν κάποια ελπίδα για τη χρήση των βιταμινών C και Ε στη θεραπεία της ημικρανίας. Μελλοντική έρευνα και τυχαιοποιημένες ελεγχόμενες δοκιμές μπορεί να βοηθήσουν στον προσδιορισμό της δοσολογίας και συγκεκριμένων ομάδων ασθενών που θα μπορούσαν να ωφεληθούν από τη συμπλήρωση βιταμινών C και Ε.

Λέξεις-κλειδιά: ημικρανία, αντιοξειδωτικά συμπληρώματα, βιταμίνη C, βιταμίνη Ε

INTRODUCTION

Migraine is a common neurological condition affecting 14% of the population.[1] Despite its prevalence, only recently have the pathophysiological mechanisms begun to be elucidated. Investigating neuroinflammation and oxidative stress in relationship to migraine provides further insights into specific pathophysiological mechanisms.[2] Within this new framework antioxidant-based mechanisms are becoming promising adjunctive therapeutic targets in migraine.[3] This narrative review will explore the role of the well-studied antioxidant vitamins C and E that may reduce oxidative damage and regulate inflammation.[4,5]

The role of oxidative stress in migraine pathophysiology

While migraine's pathophysiology is not fully understood, there are two main accepted theories: the trigeminovascular system (TGVS) and cortical spreading depression (CSD). In the TGVS model, the trigeminal nerves become activated, resulting in the release of neuropeptides, including calcitonin gene-related peptide (CGRP) and substance P, which are known mediators of neurogenic inflammation and migraine pain sensitisation. CSD is a wave of neuronal depolarisation spreading across the cortex, marked by ionic shifts and decreased brain activity. These ionic shifts increase reactive oxygen species (ROS), leading to oxidative stress and triggering pro-inflammatory pathways. Such changes may underlie the aura phase in migraine aura.[6]

Oxidative stress arises when there is an imbalance between the generation of oxidants (such as ROS) and the ability of the body to neutralise them by both enzymatic (superoxide dismutase[SOD], catalase[CAT], and glutathione peroxidase[Gpx]) and non-enzymatic (vitamin C, vitamin E, and glutathione[GSH]) antioxidants resulting in damage to important molecules such as lipid, protein, and DNA. The primary source of ROS in the brain is from mitochondria. Dysfunctional mitochondria can lead to increased levels of ROS, causing oxidative stress.[7] Additionally, migraine is associated with a specific mitochondrial disorder termed mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome which involves impaired mitochondrial function resulting in the prolonged presence of "toxic" substances, including ROS.[8] Interestingly, many recognisable migraine triggers also induce oxidative stress and are agonists of transient receptor potential cation channels, subfamily A, member 1 (TRPA1), which are located on perivascular meningeal nociceptors and second-order trigeminal neurons, detecting oxidative stress.[9,10] In animal studies, TRPA1 agonists stimulate the release of CGRP and substance P, inducing migraine attacks.[10] Oxidative stress may also be involved in cortical spreading depression (CSD) which is associated with migraine aura. Research has shown that TRPA1 activation by ROS enhances CSD, while administering antioxidants decreases the likelihood of developing CSD in vivo.[11,12] In addition, studies utilising animal models have demonstrated that CSD itself produces oxidative stress, triggering a migraine attack.[13] The role of oxidative stress in migraine pathogenesis is demonstrated in **Figure 1.**

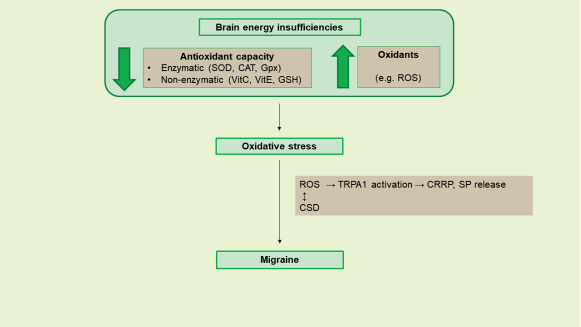

Figure 1. Schematic representation of oxidative stress role in migraine pathophysiology. SOD: superoxide dismutase; CAT: catalase; Gpx: glutathione peroxidase; VitC: vitamin C; VitE: vitamin E; GSH: glutathione; ROS: reactive oxygen species; TRPA1: transient receptor potential cation channels, subfamily A, member 1; CRRP: calcitonin gene-related peptide; SP: substance P; CSD: cortical spreading depression

Migraine is linked to brain energy insufficiencies between attacks, and these may arise from either increased energy utilisation or decreased energy production as a result of mitochondrial dysfunction.[14] Prooxidant molecules, among which are thiobarbituric acid reactive substances (TBARS), namely malonyl dialdehyde acid (MDA) and 4-hydroxynonenal, and nitric oxide have also been proposed as potential markers of oxidative stress.[15] Several research articles on oxidative stress markers in migraine individuals indicate substantial differences in redox balance compared to healthy controls (HC). Total oxidant status (TOS) and oxidative stress index (OSI) levels were elevated in migraine patients during the attack phase compared to HC.[16] Similarly, higher TOS levels were observed in patients with migraine without aura,[17] although these data were not replicated by others.[18,19] Elevated plasma MDA levels were also reported in adult migraine patients compared to controls, either during interictal periods, or independently of attack status.[20–22] On the other hand, one study of children with migraine showed significantly lower concentrations of MDA compared to HC.[23] Furthermore, some findings showed increased plasma 8-OHdG levels—more

prominently in patients with migraine without aura than in those with aura.[18] Finally, while the role of oxidative stress in migraine pathophysiology remains questionable, some interesting new evidence emerged regarding TBARS, with meta-analytic data suggesting that during attack-free periods, plasma TBARS levels were over twofold elevated in migraineurs compared to controls. The meta-analysis also suggested that individuals with migraine had increased oxidative stress due to impaired antioxidant reserves and decreased SOD activity in most studies conducted during interictal periods.[24] In addition, studies have shown that migraine patients had significantly lower GSH, glutathione-S-transferase (GST), and total antioxidant capacity (TAC) levels compared to matched controls, particularly at the ictal phases.[25] One study stated that roughly 40% of people with recurrent migraines demonstrated lower levels of TAC. Interestingly, the levels of total antioxidant status (TAS) were found lower in people with migraine without aura, although these data were not supported by a different study.[17,18] Finally, controversial data have been reported regarding levels of CAT activity in children and adolescents with migraine.[16,21,23]

Overall, these results imply that oxidative stress may be an important modulator in migraine pathophysiology and highlight antioxidant-based therapeutic strategies as potential options for migraine management.[4]

Antioxidant vitamins C and E

Dietary supplements have emerged as promising options for the management of migraine due to their antioxidant and anti-inflammatory properties.[4] Among these, vitamins C and E stand out because they have synergistic antioxidant properties; vitamin C can recycle and regenerate vitamin E from its oxidised form, thereby sustaining its protective function. Furthermore, vitamin C, being water-soluble, and vitamin E, being fat-soluble, together provide comprehensive antioxidant protection across both hydrophilic and lipophilic body compartments.[26]

Vitamin C

Vitamin C, whose active form is ascorbic acid, has a variety of biological functions. As an antioxidant, vitamin C is a high-energy electron donor to free radicals, effectively preventing free radicals from damaging cells. Moreover, it supports collagen production and helps regulate **immune responses** by reducing pro-inflammatory cytokines. In the nervous system, vitamin C contributes to the **synthesis** of **neurotransmitters** (e.g., conversion of dopamine to norepinephrine) and provides **neuroprotection** against oxidative stress.[27] The needs of Vitamin C daily intake vary by age, sex, and physiological state, and are generally in the range of 40-120 mg/day. Most can meet their daily vitamin C requirements through food, since fruits and vegetables are often a good source of vitamin C (10–100 mg/100 g).[28] Oral absorption of vitamin C is usually efficient at moderate intakes (30–180 mg per day), while levels above 1 g/day result in increasing amounts of unabsorbed vitamin C, which are eliminated in the urine. Supplementation (100–500 mg/day) may be useful in cases of deficiency, oxidative stress, or illness, though high doses (>1 g/day) offer no further benefit and may cause side effects like gastrointestinal discomfort or kidney stones.[29] Studies have demonstrated the potential benefit of using vitamin C in the treatment of a range of pathological conditions, from cancer, sepsis, and inflammation to neurological disorders such as post-shingles neuralgia, epilepsy, multiple sclerosis, and Parkinson's disease.[3,4,30,31]

Vitamin E

Vitamin E is known for its variety of biological functions. Alpha-tocopherol, the most active form, is an important antioxidant with an important function of terminating chain reactions produced by free radicals, thereby preventing lipid peroxidation and protecting cell membranes from oxidative damage. It can also inhibit the release of arachidonic acid and its enzymatic conversion to pro-inflammatory prostaglandins as part of the complex modulation of inflammatory processes.[32] In the nervous system, vitamin E helps protect from the damaging effects of excess calcium entry and lipid peroxidation.[33] The average adult's daily requirement for vitamin E is about 15 mg. Typically, a balanced diet with foods such as nuts, seeds, and vegetable oils generally supplies enough vitamin E.[34] National Institutes of Health (NIH) reports that multivitamins provide approximately 13-15 mg of vitamin E per day, while vitamin E-specific supplements often contain over 67 mg of vitamin E, which is considerably higher than the dietary requirement. The adult upper tolerable limit for vitamin E supplementation (both natural and synthetic forms) is 1,000 mg/day due to possible increased bleeding risk with higher doses. Of note, vitamin E amounts are sometimes given in International Units (IU), where 1 IU of natural vitamin E equals 0.67 mg, and 1 IU of synthetic equals 0.45 mg.[35] The protective role of vitamin E has been widely studied in conditions such as diabetes cardiovascular diseases, epilepsy and Parkinsonism.[30,33,36] **Figure 2** provides a visual summary of the mechanisms through which vitamins C and E may exert their protective effects in the context of migraine.

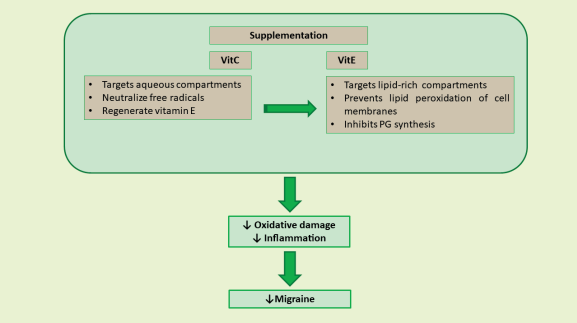

Figure 2. Representation of vitamin C and E roles in migraine treatment. VitC: vitamin C; VitE: vitamin E; PG: prostaglandin

VITAMINS C AND E IN MIGRAINE THERAPY

As more studies show that vitamin C and E supplementation can reduce markers of oxidative stress in numerous pathological conditions where inflammation and/ or oxidative stress have been implicated, the investigation of their potential role in managing migraines is promising.[37–40] The clinical studies reviewing the supplementation of vitamin C and E in migraine patients are summarised in **Table 1**.

Vitamin C

The association of vitamin C with migraine has been increasingly studied in the literature. Cross-sectional studies of American patients found that vitamin C intake was inversely associated with migraine prevalence,[41] especially in women.[42] Furthermore, other studies examined antioxidant factors, including vitamin C, reporting that higher consumption of dietary antioxidants was associated with lower migraine risk.[43–46] This finding was strongest in women of reproductive age.[43] Of note, participants benefited from moderately increased antioxidant intake, while excessive intake did not provide any additional benefit.[45,46] In addition, studies examining Iranian female patients with migraine found that increased intake of antioxidant nutrients, including vitamin C, was negatively associated with headache intensity and frequency.[47,48] Collectively, these results indicate that vitamin C may help improve migraine outcomes possibly by counteracting oxidative stress, a key factor in migraine pathophysiology, through its antioxidant properties.[3]

The positive effects of dietary vitamin C intake on migraine outcomes have prompted more research into the possible therapeutic role of vitamin C supplementation in migraine patients. Initially, Visser et al noted that the administration of vitamin C (200–1,500 mg per day) up to 50 days after wrist and ankle injury was associated with reduced incidence of complex regional pain syndrome (CRPS); given that both CRPS and migraine exhibit increased substance P and CGRP levels, as well as ROS—both disorders have been associated with neurogenic inflammation—vitamin C could be a candidate for migraine treatment as an antioxidant, as well.[49] Following this, Visser et al. conducted a (RCT) with 35 participants from Australia and evaluated the effects of NEC supplementation (600 mg N-acetylcysteine, 250 IU vitamin E, and 500 mg vitamin C) — all free radical scavengers— taken twice per day for 3 months. The NEC group (19 subjects) experienced a significant reduction in monthly headache, migraine frequency and total monthly duration, as well as pain intensity and acute abortive medication use compared to controls (16 subjects), suggesting that this antioxidant supplementation 'cocktail' may improve migraine outcomes in adults with 3 to 8 monthly migraine attacks.[50] In addition, Chayasirisobhon et al., in an uncontrolled preliminary clinical trial on 12 patients with refractory migraine in the U.S., participants received a daily antioxidant combination—120 mg pine bark extract, 60 mg vitamin C, and 30 IU vitamin E—for 3 months. Compared to their baseline, patients experienced significant decreases in headache frequency and severity.[51] Furthermore, Chayasirisobhon et al., in another uncontrolled trial involving 50 patients with chronic, treatment-resistant migraine, daily supplementation with 1,200 mg Pinus radiata bark extract plus 150 mg vitamin C over 3 months resulted in a notable decrease in headache frequency, severity, and Migraine Disability Assessment (MIDAS) scores, with sustained relief observed over a year in responders—suggesting that the antioxidant combination, including vitamin C, may help reduce migraine burden.[52] Interestingly, in a single-patient case report, an 11-year-old boy with MELAS—which is a degenerative disease attributed to oxidative phosphorylation deficiency—had decreased frequency and severity of migraine attacks following a short trial of Coenzyme Q10 (50 mg/day), vitamin B2 (100 mg twice daily), vitamin C (500 mg/day), Super B-complex with B10, alfalfa (1,000 mg/day), and a high-fat diet with 50% energy from fat.[53] Nonetheless, contrasting these positive results, a large cross-sectional study of over 15,000 adults (18-65 years) from Taiwan, Chiu et al. concluded that the use of vitamin C supplements was associated with a higher incidence of self-reported headaches or migraines among females who used these vitamin supplements compared to females who did not.[54]

In conclusion, these data indicate that vitamin C may help reduce migraine frequency and severity through its antioxidant effects. While the evidence looks promising, RCTs are needed to confirm these data.[4]

Vitamin E

Research in both humans and animals has underscored the positive effects of vitamin E on the brain and suggests that supplemental vitamin E may enhance the antioxidant capacity and help decrease oxidative stress.[33,55–57] Expanding upon this, there is a growing number of studies indicating a potential role for vitamin E in the context of migraine. In a case-control study, it was found that women with migraine had significantly lower plasma vitamin E levels compared to HC, as well as had markers indicative of increased oxidative stress. Importantly, there were no differences in vitamin E concentrations between the migraine attack and non-attack periods.[58] Similarly to vitamin C outlined above, studies showed that greater antioxidant intake, including vitamin E, was associated with a lower risk of migraine.[45,59] Of note, one study found that the strongest protective effect of dietary vitamin E against migraine frequency was observed at an intake of approximately 7.3 mg/day—beyond which no additional benefit was noted.[60] In addition to this, a reverse correlation was identified between headache frequency and consumption of increasing doses of antioxidant nutrients, among which was vitamin E.[48] Overall, these findings lend some support to the concept of a protective role of vitamin E against migraine.

Pursuant to these observational outcomes, some interventional studies specifically examined vitamin E supplementation for migraine treatments. Ziae et al. conducted a double-blind, placebo-controlled clinical trial on 72 women with menstrual migraine, using a vitamin E supplementation trial (400 units/day for 5 days beginning 2 days before menses and 3 days after, in 2 cycles), and reported a statistically significant decrease in the following migraine-related outcomes: pain severity, functional disability, photophobia, phonophobia, and nausea. This study supports a potential mechanism of vitamin E in lessening symptoms of menstrual migraines due possibly to its antioxidant properties and inhibitory effect on prostaglandin synthesis, which are thought to be involved in the pathogenesis of migraine.[61] Additionally, the previously mentioned studies by Chayasirisobhon et al. and Visser et al. found that combinations of supplements containing vitamin E reduced headache frequency, headache severity, and acute abortive medication use in migraineurs compared to controls.[50,51]

In summary, vitamin E may act as an adjunct form of antioxidant and anti-inflammatory therapy for migraines, particularly menstrual migraines.

Table 1. Summary of Clinical Studies Investigating Vitamin C and/or Vitamin E Supplementation in Patients with Migraine.

Author (Publication Year)	**Design**	**Settings**	**Intervention/Exposure**	**Participants' characteristics, N (Female%), Age**	**Results**
Visser (2020)[50]	Randomised, double-blind, sham-controlled pilot study.	Patients from Australian community.	NEC supplementation (600 mg N-acetylcysteine, 250 IU **vitamin E**, 500 mg **vitamin C**) was given twice daily for 3 months to patients with 2–8 migraines per month for at least 1 year.	NEC group=19 (89%), mean age 44.6 years Sham group=16 (81%), mean age 44.8 years	NEC treatment led to monthly reductions in migraine episodes, days, duration, intensity, and medication use.
Chiu (2014)[54]	Cross-sectional study	Representative sample from a 2005 national health survey, Taiwan.	Self-reported use of **vitamin C** and other supplements	Headache patients=3,795 (64.1%), mean age 39.2 years Headache-Free patients=11,619 (43.6%), mean age 40.7 years	Vitamin C use was associated with increased incidence of headache or migraine complaints in female participants.

Chayasirisobhon (2013) [52]	Open-label study	Outpatients, Anaheim, California, U.S.A.	1200 mg Pinus radiata bark extract and 150 mg **vitamin C** were given daily for 3 months to chronic migraineurs.	50 patients (88%), mean age 41.6 years	Twenty-nine patients (58%) showed significant improvement in MIDAS score, headache days, and severity after 3 months of treatment, with continued benefits in responders up to 12 months.
Ziae (2009)[61]	Randomised, double-blind, placebo-controlled trial	Students of Tarbiat Modarres University, Tehran, Iran	**Vitamin E** supplementation (400 IU daily for 5 days around menstruation over 2 cycles) in women with menstrual migraine	72 women, between 20-30 years old	Reduced migraine pain severity, functional disability, photophobia, phonophobia, and nausea.
Chayasirisobhon (2006) [51]	Uncontrolled, open-label study	Anaheim, California, U.S.A.	One capsule daily containing 120 mg pine bark extract, 60 mg **vitamin C**, and 30 IU **vitamin E** for 3 months in patients with chronic migraine with or without aura.	12 patients (83%), mean age 41.1 years	A significant improvement in the MIDAS score was observed after 3 months of treatment, alongside notable reductions in headache frequency and severity.
Panetta (2004) [53]	Case-report	Royal Children's Hospital and Monash Medical Centre, Melbourne, Australia	Short-term regimen including CoQ10 (50 mg/day), vitamin B2 (100 mg twice daily), **vitamin C** (500 mg/day), a Super B-complex (including B10), alfalfa (1000 mg/day), and a high-fat diet (50% calories from fat).	11-year-old male with MELAS syndrome	Reduction in the number and severity of migraine attacks.

IU: International Units; MIDAS: Migraine Disability Assessment score; CoQ10: Coenzyme Q10; MELAS: Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes. Note: Highlight in bold whether the supplement contains vitamin C and/ or vitamin E.

LIMITATIONS AND FUTURE DIRECTIONS

Although there is reasonable current evidence supporting a possible role for vitamins C and E in migraine treatment, there are important limitations to consider. First, most of the studies are observational, with many cross-sectional designs, and some evidence derives from case reports or uncontrolled, open-label studies. Importantly, in most studies, vitamins C and E were not administrated as a single intervention, but in combination with other antioxidant compounds. Therefore, it is difficult to determine the independent effect of each vitamin on migraine outcomes. To date, there is no RCT examining vitamin C- only supplementation in migraine. Only one pilot RCT has investigated a combined antioxidant regimen including vitamins C and E in migraine patients, and one double-blind RCT has assessed vitamin E supplementation specifically for menstrual migraine.[50,61]

Second, although this review has primarily focused on vitamins C and E, there are other micronutrients with antioxidant capabilities, such as riboflavin (vitamin B2), magnesium, alpha-lipoic acid, and coenzyme Q10 that have shown efficacy in the migraine setting, as indicated by several meta-analyses.[24,62,63]

Future work can help to address these limitations by implementing RCT designs that are well-designed and adequately powered, assessing both vitamins C and E as separate entities (including differences in doses and duration of treatment), and also assessing them as part of larger nutrient-based food approaches based on antioxidant consumption.

Until further evidence arises, vitamin C and E supplementation for migraine should be considered as an off-label and adjunctive treatment, at the clinician's discretion and by way of individualised patient care.

CONCLUSION

Current evidence suggests that vitamins C and E are promising adjunctive treatment options for migraine, based on their antioxidant and anti-inflammatory properties. Oxidative stress has been implicated in migraine pathophysiology, and since these two vitamins have synergistic antioxidant activities, their combined treatment effect may be more pronounced. Observational and interventional studies have shown that vitamin C and E supplementation is related to a reduction in the frequency, severity, and duration of migraine; specifically, vitamin E showed promise for menstrual migraine. Areas of uncertainty, including the dose-dependent effects and the conflicting results in certain populations, highlight the importance of future well-designed RCTs. Taking together, vitamins C and E may offer accessible and low-risk adjunctive treatments for migraine, warranting further clinical exploration.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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References

[1] Dong L, Dong W, Jin Y, et al. The Global Burden of Migraine: A 30-Year Trend Review and Future Projections by Age, Sex, Country, and Region. Pain Ther. 2025;14(1):297-315. doi:10.1007/s40122-024-00690-7

[2] Chen QW, Meng RT, Ko CY. Modulating oxidative stress and neurogenic inflammation: the role of topiramate in migraine treatment. Front Aging Neurosci. 2024;16:1455858. doi:10.3389/fnagi.2024.1455858

[3] Goschorska M, Gutowska I, Baranowska-Bosiacka I, et al. The Use of Antioxidants in the Treatment of Migraine. Antioxid Basel Switz. 2020;9(2):116. doi:10.3390/antiox9020116

[4] Hajhashemy Z, Golpour-Hamedani S, Eshaghian N, et al. Practical supplements for prevention and management of migraine attacks: a narrative review. Front Nutr. 2024;11:1433390. doi:10.3389/fnut.2024.1433390

[5] Niki E. Interaction of ascorbate and alpha-tocopherol. Ann N Y Acad Sci. 1987;498:186-199. doi:10.1111/j.1749-6632.1987.tb23761.x

[6] Frimpong-Manson K, Ortiz YT, McMahon LR, et al. Advances in understanding migraine pathophysiology: a bench to bedside review of research insights and therapeutics. Front Mol Neurosci. 2024;17:1355281. doi:10.3389/fnmol.2024.1355281

[7] Singh A, Kukreti R, Saso L, et al. Oxidative Stress: A Key Modulator in Neurodegenerative Diseases. Mol Basel Switz. 2019;24(8):1583. doi:10.3390/molecules24081583

[8] Smeitink J, Koene S, Beyrath J, et al. Mitochondrial Migraine: Disentangling the angiopathy paradigm in m.3243A>G patients. JIMD Rep. 2019;46(1):52-62. doi:10.1002/jmd2.12017

[9] Borkum JM. Migraine Triggers and Oxidative Stress: A Narrative Review and Synthesis. Headache. 2016;56(1):12-35. doi:10.1111/head.12725

[10] Fila M, Przyslo L, Derwich M, et al. The TRPA1 Ion Channel Mediates Oxidative Stress-Related Migraine Pathogenesis. Mol Basel Switz. 2024;29(14):3385. doi:10.3390/molecules29143385

[11] Jiang L, Ma D, Grubb BD, Wang M. ROS/TRPA1/

CGRP signaling mediates cortical spreading depression. J Headache Pain. 2019;20(1):25. doi:10.1186/s10194-019-0978-z
[12] Malkov A, Ivanov AI, Popova I, et al. Reactive oxygen species initiate a metabolic collapse in hippocampal slices: potential trigger of cortical spreading depression. J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab. 2014;34(9):1540-1549. doi:10.1038/jcbfm.2014.121
[13] Shatillo A, Koroleva K, Giniatullina R, et al. Cortical spreading depression induces oxidative stress in the trigeminal nociceptive system. Neuroscience. 2013;253:341-349. doi:10.1016/j.neuroscience.2013.09.002
[14] Borkum JM. Brain Energy Deficit as a Source of Oxidative Stress in Migraine: A Molecular Basis for Migraine Susceptibility. Neurochem Res. 2021;46(8):1913-1932. doi:10.1007/s11064-021-03335-9
[15] Jiménez-Jiménez FJ, Alonso-Navarro H, García-Martín E, et al. Oxidative Stress and Migraine. Mol Neurobiol. 2024;61(10):8344-8360. doi:10.1007/s12035-024-04114-7
[16] Yigit M, Sogut O, Tataroglu Ö, et al. Oxidative/antioxidative status, lymphocyte DNA damage, and urotensin-2 receptor level in patients with migraine attacks. Neuropsychiatr Dis Treat. 2018;Volume 14:367-374. doi:10.2147/ndt.s156710
[17] Alp R, Selek S, Alp SI, et al. Oxidative and antioxidative balance in patients of migraine. Eur Rev Med Pharmacol Sci. 2010;14(10):877-882.
[18] Geyik S, Altunısık E, Neyal AM, et al. Oxidative stress and DNA damage in patients with migraine. J Headache Pain. 2016;17(1). doi:10.1186/s10194-016-0606-0
[19] Eren Y, Dirik E, Neşelioğlu S, et al. Oxidative stress and decreased thiol level in patients with migraine: cross-sectional study. Acta Neurol Belg. 2015;115(4):643-649. doi:10.1007/s13760-015-0427-y
[20] Dehghani A, Phisonkunkasem T, Yilmaz Ozcan S, et al. Widespread brain parenchymal HMGB1 and NF-κB neuroinflammatory responses upon cortical spreading depolarization in familial hemiplegic migraine type 1 mice. Neurobiol Dis. 2021;156:105424. doi:10.1016/j.nbd.2021.105424
[21] Tuncel D, Tolun FI, Gokce M, et al. Oxidative stress in migraine with and without aura. Biol Trace Elem Res. 2008;126(1-3):92-97. doi:10.1007/s12011-008-8193-9
[22] Aytaç B, Coşkun Ö, Alioğlu B, et al. Decreased antioxidant status in migraine patients with brain white matter hyperintensities. Neurol Sci. 2014;35(12):1925-1929. doi:10.1007/s10072-014-1864-8
[23] Erol I, Alehan F, Aldemir D, et al. Increased vulnerability to oxidative stress in pediatric migraine patients. Pediatr Neurol. 2010;43(1):21-24. doi:10.1016/j.pediatrneurol.2010.02.014
[24] Neri M, Frustaci A, Milic M, et al. A meta-analysis of biomarkers related to oxidative stress and nitric oxide pathway in migraine. Cephalalgia Int J Headache. 2015;35(10):931-937. doi:10.1177/0333102414564888
[25] Tripathi GM, Kalita J, Misra UK. A study of oxidative stress in migraine with special reference to prophylactic therapy. Int J Neurosci. 2018;128(4):318-24. doi:10.1080/00207454.2017.1374959
[26] Hamilton IMJ, Gilmore WS, Benzie IFF, et al. Interactions between vitamins C and E in human subjects. Br J Nutr. 2000;84(3):261-7. doi:10.1017/S0007114500001537
[27] Alberts A, Moldoveanu ET, Niculescu AG, et al. Vitamin C: A Comprehensive Review of Its Role in Health, Disease Prevention, and Therapeutic Potential. Molecules. 2025;30(3):748. doi:10.3390/molecules30030748
[28] Doseděl M, Jirkovský E, Macáková K, et al. Vitamin C-Sources, Physiological Role, Kinetics, Deficiency, Use, Toxicity, and Determination. Nutrients. 2021;13(2):615. doi:10.3390/nu13020615
[29] Jacob RA, Sotoudeh G. Vitamin C function and status in chronic disease. Nutr Clin Care Off Publ Tufts Univ. 2002;5(2):66-74. doi:10.1046/j.1523-5408.2002.00005.x
[30] Korczowska-Łącka I, Słowikowski B, Piekut T, et al. Disorders of Endogenous and Exogenous Antioxidants in Neurological Diseases. Antioxid Basel Switz. 2023;12(10):1811. doi:10.3390/antiox12101811
[31] Bd YS. Relationship between Vitamin C, Mast Cells and Inflammation. J Nutr Food Sci. 2016;06(01). doi:10.4172/2155-9600.1000456
[32] Rizvi S, Raza ST, Ahmed F, et al. The role of vitamin e in human health and some diseases. Sultan Qaboos Univ Med J. 2014;14(2):e157-165.
[33] Bütün A, Nazıroğlu M, Demirci S, et al. Riboflavin and vitamin E increase brain calcium and antioxidants, and microsomal calcium-ATP-ase values in rat headache models induced by glyceryl trinitrate. J Membr Biol. 2015;248(2):205-213. doi:10.1007/s00232-014-9758-5
[34] Hantikainen E, Lagerros YT. Vitamin E - a scoping review for Nordic Nutrition Recommendations 2023. Food Nutr Res. 2023;67. doi:10.29219/fnr.v67.10238
[35] National Institutes of Health. Office of Dietary Supplements. Vitamin E: Fact Sheet for Con-

sumers. Office of Dietary Supplements Fact Sheets. March 22, 2021. Accessed August 4, 2025. https://ods.od.nih.gov/factsheets/VitaminE-Consumer/

[36] Chang MC, Kwak SG, Kwak S. Effect of dietary vitamins C and E on the risk of Parkinson's disease: A meta-analysis. Clin Nutr Edinb Scotl. 2021;40(6):3922-3930. doi:10.1016/j.clnu.2021.05.011

[37] Kim M, Eo H, Lim JG, et al. Can Low-Dose of Dietary Vitamin E Supplementation Reduce Exercise-Induced Muscle Damage and Oxidative Stress? A Meta-Analysis of Randomized Controlled Trials. Nutrients. 2022;14(8):1599. doi:10.3390/nu14081599

[38] Righi NC, Schuch FB, De Nardi AT, et al. Effects of vitamin C on oxidative stress, inflammation, muscle soreness, and strength following acute exercise: meta-analyses of randomized clinical trials. Eur J Nutr. 2020;59(7):2827-2839. doi:10.1007/s00394-020-02215-2

[39] Vogli S, Naska A, Marinos G, et al. The Effect of Vitamin E Supplementation on Serum Aminotransferases in Non-Alcoholic Fatty Liver Disease (NAFLD): A Systematic Review and Meta-Analysis. Nutrients. 2023;15(17):3733. doi:10.3390/nu15173733

[40] Bayu P, Wibisono JJ. Vitamin C and E antioxidant supplementation may significantly reduce pain symptoms in endometriosis: A systematic review and meta-analysis of randomized controlled trials. PloS One. 2024;19(5):e0301867. doi:10.1371/journal.pone.0301867

[41] Zhao D, Long X, Wang J. Association between dietary vitamin C intake and migraine in adults: A cross-sectional study of the National Health and Nutrition Examination Survey. J Hum Nutr Diet Off J Br Diet Assoc. 2024;37(6):1454-1464. doi:10.1111/jhn.13366

[42] Zheng Y, Jin J, Wei C, et al. Association of dietary vitamin C consumption with severe headache or migraine among adults: a cross-sectional study of NHANES 1999-2004. Front Nutr. 2024;11:1412031. doi:10.3389/fnut.2024.1412031

[43] Li Z, Zhang X, Kong S, et al. Association between composite dietary antioxidant index and migraine in American young women: insights from NHANES 1999-2004 cross-sectional data. Front Neurol. 2024;15:1399916. doi:10.3389/fneur.2024.1399916

[44] Liu X, Liu R, Liu W, et al. Association between oxidative balance score and self-reported severe headache or migraine based on NHANES 1999 to 2004 data: A cross-sectional study. Heliyon. 2024;10(6):e27426. doi:10.1016/j.heliyon.2024.e27426

[45] Zhang Z, Chen X, Fang H, et al. Association between the Composite Dietary Antioxidant Index and severe headache or migraine: results from the National Health and Nutrition Examination Survey. Front Neurol. 2024;15:1407243. doi:10.3389/fneur.2024.1407243

[46] Zuo T, Yang J, Sun Y, et al. A U-shaped association between composite dietary antioxidant index and migraine in US adults: a nationwide cross-sectional study. Nutr Neurosci. 2025;28(7):796-806. doi:10.1080/1028415X.2024.2423574

[47] Bahrampour N, Mirzababaei A, Yarizadeh H, et al. The relationship between dietary nutrients patterns and intensity and duration of migraine headaches. Br J Nutr. Published online January 17, 2022:1-8. doi:10.1017/S0007114522000046

[48] Hajishizari S, Mirzababaei A, Abaj F, et al. The association between dietary antioxidant quality score and intensity and frequency of migraine headaches among women: a cross-sectional study. BMC Womens Health. 2024;24(1):497. doi:10.1186/s12905-024-03260-3

[49] Visser EJ. Is migraine a complex regional pain syndrome of the brain? Migraine prophylaxis with vitamin C? Pain Pract Off J World Inst Pain. 2011;11(2):199-200. doi:10.1111/j.1533-2500.2011.00442.x

[50] Visser EJ, Drummond PD, Lee-Visser JLA. Reduction in Migraine and Headache Frequency and Intensity With Combined Antioxidant Prophylaxis (N-acetylcysteine, Vitamin E, and Vitamin C): A Randomized Sham-Controlled Pilot Study. Pain Pract Off J World Inst Pain. 2020;20(7):737-747. doi:10.1111/papr.12902

[51] Chayasirisobhon S. Use of a pine bark extract and antioxidant vitamin combination product as therapy for migraine in patients refractory to pharmacologic medication. Headache. 2006;46(5):788-793. doi:10.1111/j.1526-4610.2006.00454.x

[52] Chayasirisobhon S. Efficacy of Pinus radiata bark extract and vitamin C combination product as a prophylactic therapy for recalcitrant migraine and long-term results. Acta Neurol Taiwanica. 2013;22(1):13-21.

[53] Panetta J, Smith LJ, Boneh A. Effect of high-dose vitamins, coenzyme Q and high-fat diet in paediatric patients with mitochondrial diseases. J Inherit Metab Dis. 2004;27(4):487-498. doi:10.1023/B:BOLI.0000037354.66587.38

[54] Chiu HY, Tsai PS, Lee CC, et al. The association between use of dietary supplements and headache or migraine complaints. Headache. 2014;54(2):355-363. doi:10.1111/head.12180

[55] Nazıroğlu M, Çelik Ö, Uğuz AC, et al. Protective

Effects of Riboflavin and Selenium on Brain Microsomal Ca2+-ATPase and Oxidative Damage Caused by Glyceryl Trinitrate in a Rat Headache Model. Biol Trace Elem Res. 2015;164(1):72-79. doi:10.1007/s12011-014-0199-x

[56] Das Evcimen N, Ulusu NN, Karasu C, et al. Adenosine triphosphatase activity of streptozotocin-induced diabetic rat brain microsomes. Effect of vitamin E. Gen Physiol Biophys. 2004;23(3):347-355.

[57] Kayan M, Nazıroğlu M, Ovey IS, et al. Non-ionic contrast media induces oxidative stress and apoptosis through Ca^{2+} influx in human neutrophils. J Membr Biol. 2012;245(12):833-840. doi:10.1007/s00232-012-9491-x

[58] Armağan HH, Karaman K, Yalçın Yılmaz D. Antioxidant and cytokine levels in plasma of patients with attack and non-attack periods. J Cell Neurosci Oxidative Stress. 2020;12(1):914-921. doi:10.37212/jcnos.806797

[59] Li Z, Fan Z, Zhang Q. The Associations of Phosphorylated Tau 181 and Tau 231 Levels in Plasma and Cerebrospinal Fluid with Cognitive Function in Alzheimer's Disease: A Systematic Review and Meta-Analysis. J Alzheimers Dis JAD. 2024;98(1):13-32. doi:10.3233/JAD-230799

[60] Wu W, Peng Y, Chen S. L-shaped relationship between dietary vitamin E intake and migraine in adults: a cross-sectional analysis of NHANES 1999-2004. Front Neurol. 2025;16:1582379. doi:10.3389/fneur.2025.1582379

[61] Ziaei S, Kazemnejad A, Sedighi A. The effect of vitamin E on the treatment of menstrual migraine. Med Sci Monit Int Med J Exp Clin Res. 2009;15(1):CR16-19.

[62] Talandashti MK, Shahinfar H, Delgarm P, et al. Effects of selected dietary supplements on migraine prophylaxis: A systematic review and dose-response meta-analysis of randomized controlled trials. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol. 2025;46(2):651-670. doi:10.1007/s10072-024-07794-0

[63] Parohan M, Sarraf P, Javanbakht MH, et al. Effect of coenzyme Q10 supplementation on clinical features of migraine: a systematic review and dose-response meta-analysis of randomized controlled trials. Nutr Neurosci. 2020;23(11):868-875. doi:10.1080/1028415X.2019.1572940